Translation obtained from Japanese Patent Office website

PATENT ABSTRACTS OF JAPAN

(11)Publication number : **10-101576**

(43)Date of publication of application : **21.04.1998**

2/5/04 SWB

(51)Int.CI. A61K 38/26

A61K 31/195

A61K 38/00

(21)Application number : **08-260683**

(22)Date of filing : **01.10.1996**

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(54) TREATING MEDICINE FOR DIGESTIVE ORGAN DISEASE

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain the subject medicine which promotes the multiplication of gastrointestinal mucosa and can display excellent effect for treatment of digestive organ diseases, for example, for recovery of gastrointestinal injury, by using glicentin and glutamine (derivative) in combination.

SOLUTION: This medicine contains (A) glicentin and (B) glutamine (derivative) as an active ingredient. As glutamine derivatives in the ingredient B, an acylglutamine (preferably acetylglutamine), a dipeptide or a tripeptide containing glutamine and an oligopeptide containing glutamine (preferably wheat protein) are preferable. By this active ingredient, safe and objective effects are expectable.

LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

CLAIMS

[Claim(s)]
[Claim 1] (a) A digestive system disease therapy agent which contains a glicentin and the (b) glutamine, or a glutamine derivative as an active principle.
[Claim 2] A digestive system disease therapy agent of claim 1 whose glutamine derivative is an acyl glutamine, glutamine content G, the Tori-peptide, or glutamine content oligopeptide.
[Claim 3] A digestive system disease therapy agent according to claim 2 whose acyl glutamine is an acetyl glutamine.
[Claim 4] A digestive system disease therapy agent according to claim 2 whose glutamine content G peptides are L-alanyl-L-glutamine, an L-glutamyl-L-alanine, glycyl-L-glutamine, an L-glutamyl-L-glycine, and L-glutamyl-L-glutamine.
[Claim 5] A digestive system disease therapy agent according to claim 2 from which glutamine content oligo ** PUCHIDO is obtained by hydrolyzing wheat protein in enzyme.
[Claim 6] A digestive system disease therapy agent according to claim 2 whose digestive system diseases are ulcerousness or an inflammatory digestive system disease, and a digestive system disease resulting from abnormalities native, or an acquired digestion failure or membrane penetrable.
[Claim 7] A digestive system disease therapy agent according to claim 6 which is a thing accompanying [an acquired digestion failure is based on damage on an alimentary canal based on alimentary canal excision, radiation injury, and a drugs failure, and] an intravenous nutrition method or tube feeding.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] This invention relates to use of the glicentin as the digestive system disease therapy agent which contains the (a) glicentin and the (b) glutamine, or a glutamine derivative as an active principle, and a digestive system disease therapy agent by promoting growth of digestive organ membrane by medicating a list with the (a) glicentin and the (b) glutamine, or a glutamine derivative and a glutamine, or a glutamine derivative. Moreover, the symptom of gastrointestinal motility is related with use of the (a) glicentin as an alimentary canal disease therapy agent for promoting an improvement or recovery and the (b) glutamine, or a glutamine derivative by delaying migration of alimentary canal contents.
[0002]
[Description of the Prior Art] It is found out by this invention persons that it is useful as drugs which promote growth of a digestive system disease therapy agent and digestive organ membrane, and the glicentin which is one of the enteroglucagons and is the peptide which has 69 amino acid residue is indicated at JP,7-223967,A.
[0003] moreover, under the stress at the time of starvation and surgical invasion etc., if the need of the glutamine in an intestinal tract grows and a glutamine is not given from the exterior, a glutamine will supply by decomposition of the muscular system -- having -- the lack of a systemic glutamine -- being generated -- just -- being alike -- villus withering in intestines is invited and it is known that the function of an intestinal tract will fall. To and a recovery of the wound of an alimentary canal, withering of alimentary canal membrane, a digestive tract function failure, etc., and prevention sake The amino acid infusion solution which importance of a glutamine is clarified and contains the dipeptide of a glutamine and a glutamine to JP,3-264525,A A peptide constituent with the high glutamine content as an oral feeding agent to JP,5-236909,A The method of increasing the gastrointestinal absorption which consists of prescribing for the patient what combined the glutamine or a glutamine equivalent and a growth hormone, the insulin-like growth factor, etc. in a ****** No. 501796 [seven to] official report The malfunction of the intestinal mucosa which prescribes for the patient a glutamine and the constituent with which short **** consists of medium chain fatty acid, a growth hormone, etc., or the therapy method of a disease is indicated by the ****** No. 500109 [six to] official report.
[0004]
[Problem(s) to be Solved by the Invention] And, the wound of an alimentary canal useful as drugs with which a glicentin promotes growth of a digestive system disease therapy

agent and digestive organ membrane as described above, Although it is known that a glutamine or a glutamine derivative is useful for recovery of withering of alimentary canal membrane, a digestive tract function failure, etc. and prevention In order to use it individually as glicentin pharmaceutical preparation or glutamine pharmaceutical preparation, respectively, it was inquired and developed, and independent use of each pharmaceutical preparation was carried out, and it was the thing which stops at attaining the drug effect expected by it from each pharmaceutical preparation. However, the cause of a digestive system disease is made many more from various factors, such as complication of modern society, increase of stress, and a medical advancement. moreover, about the therapy agent used for the therapy of a digestive system disease by complication of a cure What can expect a more advanced curative effect is called for and, moreover, safety comes to be thought as important much more. About the existing safety, it is the pharmaceutical preparation which is check ending, and development of the drugs which the remarkable effect which was not moreover able to be attained depending on independent use of these pharmaceutical preparation can attain is just going to be called for.

[0005]

[Means for Solving the Problem] When this invention persons used wholeheartedly as a result of research that the above-mentioned technical problem should be solved, combining both the (a) glicentin, (b) glutamine, or glutamine derivative also unexpectedly, they found out that an effect remarkable in a therapy of digestive system diseases, such as promotion and the recovery of damage of an alimentary canal, was acquired in growth of alimentary canal membrane as compared with a case where a glicentin, a glutamine, or a glutamine derivative is used independently, and completed this invention.

[0006] That is, this invention relates to a digestive system disease therapy agent which contains the (a) glicentin and the (b) glutamine, or a glutamine derivative as an active principle. In this invention to a glutamine derivative An acyl glutamine, glutamine content G, or the Tori-peptide, Glutamine content oligopeptide etc. is contained. As this acyl glutamine or concretely An acetyl glutamine, a propanoyl glutamine, a butanoyl glutamine, etc. are mentioned. As a glutamine content G peptide L-alanyl-L-glutamine, an L-glutamyl-L-alanine, L-glycyl-L-glutamine, An L-glutamyl-L-glycine, L-glutamyl-L-glutamine, etc. are mentioned. As a glutamine content Tori-peptide An L-glutamyl-L-glutamyl-L-alanine, L-glutamyl-L-glycyl-L-glutamine, L-alanyl-L-glutamyl-L-glutamine, an L-glycyl-L-glutamyl-L-alanine, etc. are mentioned. furthermore, as an example of glutamine content oligo ** PUCHIDO What [what hydrolyzed wheat protein in enzyme and was obtained], for example, a thing manufactured by method indicated by Japanese Patent Application No. No. (JP,6-245790,A) 61298 [five to] concerning application of these people, That is, oligopeptide mixture obtained by hydrolyzing for 5 to 30 hours using alkaline protease to which the Bacillus bacteria produce wheat protein at pH 8.0-11.0 and temperature of 40-70 degrees C can be mentioned. And a glutamine is contained in this oligopeptide in 30% of the weight or more of an amount.

[0007] A digestive system disease therapy agent of this invention is used for a therapy of various digestive system diseases, for example, ulcerousness, or an inflammatory digestive system disease, and a digestive system disease by abnormalities native, or an acquired digestion failure or membrane penetrable.

[0008] A peptic ulcer, and a sore and an acute ulcer, i.e., an acute membrane lesion, are included in an ulcer disease of a digestive organ described here. Moreover, a glicentin has an operation which promotes growth of intestinal mucosa, and since a glutamine has an intestinal-mucosa degeneracy control function, a digestive system disease therapy agent of this invention becomes in it that it is possible in using to an improvement of hypoplasia of a therapy of digestion, a therapy to symptoms of absorption incompetence, and prevention, i.e., membrane withering, and prevention, or an alimentary canal organization, and an improvement of a digestion function. Furthermore, it is useful also for a therapy of membrane symptoms by inflammatory diseases, such as enteritis, Crohn's disease, and ulcerative colitis, and a therapy of a damping syndrome etc.

[0009] Moreover, a digestive system disease therapy agent of this invention is based on a therapy when digestive organ organizations, such as the stomach, the duodenum, a small intestine, or the large intestine, decrease in number, promotion of recovery, for example, surgery excision, of an alimentary canal with surgical invasion like alimentary canal excision, and radiation, or is used also for a therapy of a digestive system disease by alimentary-canal membrane withering which is a thing accompanying a therapy, an intravenous nutrition method, or tube feeding of damage of a blemish by drugs on a carrier beam alimentary canal, or acquired digestion failure

[0010] a glicentin of one component of a digestive system disease therapy agent of this invention can fluctuate that dose suitably with a symptom of a patient who should prescribe a medicine for the patient, age, sex, weight, etc., and it is an administration gestalt of this digestive system disease therapy agent, i.e., internal use, -- or it differs by whether it is parenteral administration. Usually, to an adult, 0.05mg per cannot be found and 100mg (0.1mg per thru/or 20mg) of glicentins can be preferably prescribed for the patient day day.

[0011] moreover, a glutamine or a glutamine derivative which is one [of a digestive system disease therapy agent of this invention] of other components can also fluctuate that dose suitably with a symptom of a patient who should prescribe a medicine for the patient, age, sex, weight, etc., and is an administration gestalt of this digestive system disease therapy agent, i.e., internal use, -- or it differs by whether it is parenteral administration. Usually, to an adult, as a glutamine, 0.5g per cannot be found and 90g is preferably prescribed for the patient in an amount of 3g per thru/or 70g day day. As internal use pharmaceutical preparation, a medicine can be prescribed for the patient with a gestalt of aquosity, an oleaginous solution or suspension, an emulsion, a granule, a tablet, or freezing powder.

[0012] Although a digestive system disease therapy agent of this invention consists of two active principles as described above, and these components are made to usually exist in a form mixed in one pharmaceutical preparation It is necessarily unnecessary to exist in a form mixed in 1 agent. Since same drug effect is done so also by medicating coincidence with both, a digestive system disease therapy agent of this invention may be the thing of dosage forms which combined a glicentin and a glutamine, or a glutamine derivative in a form of a pharmaceutical preparation kit. or [namely, / that can be-izing / a glicentin / as glicentin pharmaceutical preparation / and a glutamine or a glutamine derivative can be separately pharmaceutical-preparation-ized as glutamine pharmaceutical preparation in this case, and both administration gestalt is the same] -- or you may differ, and both can be prescribed for the patient in taking orally, a medicine can

be parenterally prescribed for the patient, or others one of the two in taking orally can also be parenterally prescribed for the patient for one of the two.
[0013] Since a glicentin is a polypeptide as described above, and an alimentary canal disease therapy agent containing a glicentin of this invention removes a case where a direct action is carried out within the stomach and can consider a fall of the activity by denaturation by acid in the stomach and decomposition by digestion, and denaturation when prescribing this for the patient in taking orally, it is desirable to take into consideration emission of an active principle in an intestinal tract by enteric coating. Therefore, about a case where an alimentary canal disease therapy agent of this invention is administered orally, it is desirable to coat by well-known enteric coating agent. Thus, except for a case where it is made to act on gastric mucosa directly in the stomach, an active principle will be emitted for the first time in an intestinal tract, and an alimentary canal disease therapy agent of this invention to which enteric coating was performed will act on intestinal mucosa.
[0014] OIDORAGITTO and a semi-synthetic polymer compound, for example, cellulose acetate phthalate, with which what was ordinarily known for this technical field as a coating agent for manufacturing this enteric agent is available, and uses a synthetic high polymer, for example, polyacrylate, as a principal component, and a natural product metaphor can use a shellac etc. However, an administration means by parenteral administration is desirable as a means to medicate the body with a glicentin, without receiving denaturation or decomposition. There is a method by method of prescribing for the patient with subcutaneous injection, an intravenous injection, an intramuscular injection, intraperitoneal injection, or an infusion solution and intubation, and enteral administration in this parenteral administration.
[0015] A glicentin used in this invention is shown by the following amino acid sequence. Arg-Ser-Leu-Gln-Asp-Thr-Glu-Glu-Lys-Ser-Arg-Ser-Phe-Ser-Ala-Ser-Gln-Ala-Asp-Pro-Leu-Ser-Asp-Pro-Asp-Gln-Met-Asn-Glu-Asp-Lys- Arg-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg -Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala [0016] Moreover, a glicentin which a methionine added can be similarly used for N-end in this invention. This N-end methionine addition glicentin is shown by the following amino acid sequence. Met-Arg-Ser-Leu-Gln-Asp-Thr-Glu-Glu-Lys-Ser-Arg-Ser-Phe-Ser-Ala-Ser-Gln-Ala-Asp-Pro-Leu-Ser-Asp-Pro-Asp-Gln-Met-Asn-Glu-Asp- Lys-Arg-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-A rg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-Lys-Arg-Asn-Arg-Asn-Asn-Ile-Ala [0017] These glicentins or N-end methionine addition glicentin can be manufactured with the gene engineering-technique or a synthesis method using the corresponding gene of a DNA array. As an example of this gene engineering-technique, it is indicated in JP,4-364199,A concerning this invention persons' invention, and a method is mentioned.
[0018] Although an example and an example of pharmaceutical preparation explain this invention further below at details, these are all for explaining this invention, and do not limit this invention.
[0019]
[Example]
an example 1 -- this example is for showing clearly what kind of recovery the intestinal tract of the laboratory animal which received damage shows as compared with the case of

not prescribing a medicine for the patient, when independent administration of a glicentin and the glutamine is carried out, respectively, and when both glicentin and glutamine are prescribed for the patient. In this example, 41 SD system male rats (weight of 200g) were divided into five groups, in MTX the control group non-prescribing a medicine for the patient, and the second group (nine animals), a glicentin independent administration group and the fourth group (eight animals) made it as the glicentin and the glutamine administration group, and the fifth group (eight animals) made a MTX administration control group and the third group the glutamine independent administration group for the first group (eight animals). These rats were bred in the individual cage and 15g per one per day fed Elental (R) and (the component nutrient of Morishita RUSERU, Inc.) which dissolved in water. In addition, MTX is the cable address of methotrexate (N-[4-[[(2, 4-diamino-6-PUTERIJINIRU) methyl] methylamino] benzoyl]-L-glutamic acid). About the second group, it medicated the intraperitoneal one between 1-time three-day days with MTX of 10 mg/kg per day eight days after feed initiation. About the third group, hypodermically was medicated with the glicentin of 200microper day g in 2 steps every day at feed initiation and coincidence per animal, and it medicated the intraperitoneal one between 1-time three-day days with MTX of 10 mg/kg with the glicentin eight days after feed initiation further. About the fourth group, hypodermically was medicated with the glicentin of 200microper day g in 2 steps every day at feed initiation and coincidence per animal, and the 1.2g [per day] glutamine was administered orally in 2 steps every day, and it medicated the intraperitoneal one between 1-time three-day days with MTX of 10 mg/kg with the glicentin and the glutamine eight days after feed initiation further. About the fifth group, the 1.2g [per day] glutamine was administered orally to feed initiation and coincidence in 2 steps every day per animal, and it medicated the intraperitoneal one between 1-time three-day days with MTX of 10 mg/kg with the glutamine eight days after feed initiation further. Bleeding death was carried out about the trial animal of the above-mentioned first - the fifth group on the next day [of MTX administration termination], from a TORAITSU ligament to the ileocecum was extracted, and the physiological saline washed the inside of a lumen. Where the load of the 10g weight is carried out to an intestinal tract, the overall length was equally divided into two, the upper part was made into jejunum, the lower part was made into the ileum, membrane was scraped with slide glass, and weight was measured. The data of the trial animal of the first about the weight of ileal mucous membrane - the fifth group is shown in a table 1, and the data of the trial animal of the first about the weight of jejunal mucous membrane - the fifth group is shown in a table 2.

[0020]

[A table 1]

表 1

	第一群	第二群	第三群	第四群	第五群
動物数	8	9	8	8	8
回腸粘膜平均重量(g)	0.721±0.029	0.382±0.015	0.407±0.020	0.453±0.027	0.387±0.010

The average weight of the fourth group is significant at 5% of level of significance to the second group.

[0021]

[A table 2]

表 2

	第一群	第二群	第三群	第四群	第五群
動物数	8	9	8	8	8
空腸粘膜平均重量(g)	1.454±0.070	0.829±0.017	0.871±0.022	1.030±0.023	0.893±0.042

The average weight of the fourth group is significant at 0.5% of level of significance to the second group.

[0022] By medicating a rat with MTX as a result of the above-mentioned trial, in the ileum, reduction of the membrane weight to 57% was seen, and was seen by jejunum 53%. This experiment showed that a glicentin administration group showed recovery orientation to membrane weight by jejunum and the ileum, and recovery orientation was shown in membrane weight by jejunum by the glutamine administration group. And it turns out that significant recovery will be seen also in any of jejunum and an ileum if a glicentin and a glutamine are used together, and the multiplication-effect far exceeding the additive effect expected from the effect acquired by both independent administration is acquired.

[0023] an example 2 -- this example is for clarifying recovery orientation from damage on an intestinal tract by measuring of what kind of amount the intestinal tract of the laboratory animal which received damage holds DNA in that membrane as compared with the case of not prescribing a medicine for the patient, when independent administration of a glicentin and the glutamine is carried out, respectively, and when both glicentin and glutamine are prescribed for the patient. In this example, 33 SD system male rats (weight of 200g) were divided into four groups, a glicentin independent administration group and the third group (eight animals) made it as the glicentin and the glutamine administration group, and the fourth group (eight animals) made a control group and the second group (eight animals) the glutamine independent administration group for the first group (nine animals). These rats were bred in the individual cage and 15g per one per day fed Elental (R) dissolved in water. About the first group, it medicated the intraperitoneal ones between 1-time three-day days with MTX of 10 mg/kg per day eight days after feed initiation. About the second group, hypodermically was medicated with the glicentin of 200microper day g in 2 steps every day at feed initiation and coincidence per animal, and it medicated the intraperitoneal one between 1-time three-day days with MTX of 10 mg/kg with the glicentin eight days after feed initiation further. About the third group, hypodermically was medicated with the glicentin of 200microper day g in 2 steps every day at feed initiation and coincidence per animal, and the 1.2g [per day] glutamine was administered orally in 2 steps every day again, and it medicated the intraperitoneal one between 1-time three-day days with MTX of 10 mg/kg with the glicentin and the glutamine eight days after feed initiation further. About the fourth group, 1.2g [per day] GURUTAMIN ** was administered orally to feed initiation and coincidence in 2 steps every day per animal, and it medicated the intraperitoneal one between 1-time three-day days with MTX of 10 mg/kg with the glutamine eight days after feed initiation further. Bleeding death was carried out about the trial animal of the above-mentioned first - the fourth group on the next day [of MTX administration termination], from a TORAITSU ligament to the ileocecum was extracted, and the

physiological saline washed the inside of a lumen. Where the load of the 10g weight is carried out to an intestinal tract, the overall length was equally divided into two, the upper part was made into jejunum, the lower part was made into the ileum, and membrane was scraped and taken out with slide glass. The membrane of jejunum and an ileum part was suspended in phosphate buffered saline (20ml and 10ml), respectively, by the bottom ultrasonic wave crusher of ice-cooling, was processed for 30 seconds and carried out ize [HOMOJIE]. Homogenate was diluted with this buffer solution 5 times, and was used for the quantum of DNA. RNase which added the 0.9ml 0.1M tris hydrochloric-acid buffer solution pH 8.8 to 0.1ml of samples obtained by the above-mentioned actuation, and was beforehand prepared in concentration of 10mg/ml with these tris buffers Type I-A (sigma company) was 20microl Added, and it was made to react at 50 degrees C for 1 hour. 1ml of 20microg [/ml] ethidium bromide solutions prepared with distilled water was added, and fluorescence with a wavelength [when exciting by ultraviolet rays with a wavelength of 365nm] of 590nm was measured. From the calibration curve created using the 100microg [/ml] known concentration DNA from 10, the ileum and the amount of DNA of jejunal mucous membrane were computed in quest of the DNA concentration in a sample. It asked for DNA concentration according to J.Lab.Clin.Med. (1972), 80, and the method indicated by 598-602. The data of the trial animal of the first about the amount of DNA of ileal mucous membrane - the fourth group is shown in a table 3, and the data of the trial animal of the first about the amount of DNA of jejunal mucous membrane - the fourth group is shown in a table 4.

[0024]

[A table 3]

Ileal

	第一群	第二群	第三群	第4群
動物数	9	8	8	8
回腸粘膜 DNA量(mg)	1.306±0.069	1.370±0.126	1.648±0.146	1.364±0.092

The amount of DNA of the third group is significant at 5% of level of significance to the first group.

[0025]

[A table 4]

Jejunal

	第一群	第二群	第三群	第4群
動物数	9	8	8	8
空腸粘膜 DNA量(mg)	3.372±0.164	3.829±0.185	4.696±0.198	3.954±0.242

The amount of DNA of the third group is significant at 0.5% of level of significance to the first group.

[0026] Although the amount of DAN(s) in jejunum and ileal mucous membrane shows a slightly high value by the glicentin administration group and the glutamine administration group from this experiment as compared with it of a MTX administration group, it turns out by the concomitant use administration group of a glicentin and a glutamine that the amount of DAN(s) in jejunum and ileal mucous membrane is a remarkable high value.

[0027] The example of pharmaceutical preparation of the digestive system disease therapy agent of this invention is shown below.
Example of pharmaceutical preparation One glicentin 5g, acetyl glutamine 1kg, 2kg [of lactoses], 20g [of magnesium stearates], and corn-starch 100g was mixed, the mixture which compressed and compressed this mixture was ground, and mixture granulatio was prepared. The obtained granulatio was covered over the tableting machine and the tablet which contains glicentin 2.5microg and acetyl glutamine 0.5g per one lock was obtained. In order to make this tablet enteric, enteric coating was performed to the tablet by cellulose acetate phthalate.
[0028] Example of pharmaceutical preparation Two glicentin 1g, glutamine 500g, and 100g of lactoses were mixed, it dissolved in 1l. of distilled water for injection, this solution was filtered with sterile 0.22-micrometer membrane filter, 1ml was poured distributively into each vial bottle in sterile, contents were freeze-dried, and the pharmaceutical preparation for injection was prepared.
[0029] Example of pharmaceutical preparation Three glicentin 1g and dipeptide (what consists of L-alanyl-L-glutamine and L-glutamyl-L-alanine) 1kg of a glutamine were dissolved in 1l. of distilled water for injection, 3g of sodium hydrogensulfites was added as a stabilizer, and pH was adjusted to 7.0 with the acetic acid. Subsequently, this solution was filtered with sterile 0.22-micrometer membrane filter, it poured distributively into the vial bottle in sterile, and the infusion solution which replaces with nitrogen gas and contains a glicentin and a glutamine dipeptide was prepared.

[Translation done.]